

# Polycystic Ovary Syndrome and the Metabolic Syndrome

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Diabetologists have long recognized the comorbid diseases of obesity, hypertension, and hyperlipidemia in their type 2 diabetic patients, and the necessity of treating these conditions in order to improve outcomes. Cardiovascular disease (CVD) is the number-one cause of death among patients with diabetes, and its prevention is at the forefront of modern diabetes care. The clustering of insulin resistance, obesity, hypertension, and dyslipidemia has been termed “the metabolic syndrome.”

As national attention is focused on the emerging epidemic of type 2 diabetes and obesity, more energy is being directed toward earlier detection, improved therapies, and potential prevention. One condition commonly detected in a younger age group and associated with a high risk of progression to diabetes is polycystic ovary syndrome (PCOS). Interestingly, many of the features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemias, are also present in PCOS. Is PCOS an early manifestation of the metabolic syndrome?

## Recent Developments Regarding the Metabolic Syndrome

The metabolic syndrome is composed of abnormalities that increase cardiovascular risk. Although each constituent condition is associated with heart disease in its own right, the combination of these conditions far more powerfully augments cardiovascular risk.

The metabolic syndrome was recently codified in the National Cholesterol Education Program Adult Treatment

Panel III (NCEP ATP-III) guidelines, but has long been the subject of extensive research and debate. The NCEP definition includes fasting glucose, waist circumference, blood pressure, and lipid criteria pertaining to triglycerides and HDL cholesterol.<sup>1</sup> An earlier definition by the World Health Organization (WHO) relied more heavily on insulin resistance as a necessary component of the metabolic syndrome<sup>2</sup> and was thus closer to the original description of the “insulin resistance syndrome” or “syndrome X” within the diabetic population.<sup>3</sup> Definitions of the metabolic syndrome are summarized in Table 1.

A major advantage of the NCEP definition is its ease of application. For instance, while neither sensitive nor specific as an indicator of insulin resistance, fasting glucose testing identifies further developed abnormalities of glucose regulation and can readily be performed in clinical practice and large clinical trials. For the WHO definition, measurement of insulin resistance requires a cumbersome clamp study, which has confounded its use. Thus, major epidemiological

studies such as the European Group for the Study of Insulin Resistance and the Botnia study in Finland and Sweden used widely applicable surrogate markers of insulin resistance, such as fasting glucose and insulin levels,<sup>4</sup> or glucose tolerance tests.<sup>5</sup> Additionally, newer data have allowed subtle refinements in cut-off criteria based on outcomes research. Just as the blood glucose level used to define diabetes was lowered in 1997 based on outcomes,<sup>6</sup> definitions of hypertension in the metabolic syndrome have recently been lowered.<sup>7</sup> Finally, waist circumference has replaced BMI as a marker of obesity because of its better correlation with intra-abdominal visceral adipose tissue and worsened cardiovascular outcomes.<sup>8</sup>

Using data from the Kuopio Finnish cohort, the NCEP ATP-III and the WHO modified definitions of the metabolic syndrome were both validated in a large epidemiological study that found up to four times higher coronary heart disease (CHD) mortality in patients with the metabolic syndrome.<sup>9</sup>

The stated purposes of the NCEP ATP-III guidelines were to maintain the original ATP-I and -II goal of primary prevention of CHD in people with high LDL cholesterol with the new focus on people with multiple risk factors, such as those with the metabolic syndrome.<sup>1</sup> Women with PCOS are such a group.

## What is PCOS?

PCOS is familiar to internists and diabetologists because of its frequent occurrence as a precursor to diabetes. PCOS is clinically defined as oligomenorrhea associated with hyperandro-

### IN BRIEF

Many patients with polycystic ovary syndrome (PCOS) also have features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemia, suggesting an increased risk for cardiovascular disease. Increased awareness of this overlap advocates therapies that improve insulin resistance and often ameliorate PCOS symptoms.

**Table 1. Definitions of the Metabolic Syndrome**

<b>NCEP</b>	<b>WHO</b>	<b>WHO modified*</b>
<b>Any three of the following criteria:</b> Fasting plasma glucose $\geq 110$ mg/dl	Insulin resistance (under hyperinsulinemic, euglycemic conditions)	Hyperinsulinemia: upper quartile of population <b>or</b> fasting plasma glucose $\geq 110$ mg/dl
Hypertension $\geq 130$ mmHg systolic or $\geq 85$ mmHg diastolic blood pressure	<b>Plus any two of the following criteria:</b> Hypertension $> 160/90$ mmHg or controlled with drug treatment	<b>Plus any two of the following criteria:</b> Hypertension $\geq 140/90$ mmHg or controlled with drug treatment
Obesity Waist circumference $> 40$ inches for males, $> 35$ inches for females	Obesity BMI $> 30$ kg/m <sup>2</sup> <b>or</b> waist-to-hip ratio $> 0.9$ for males, $> 0.85$ for females	Obesity BMI $\geq 30$ kg/m <sup>2</sup> <b>or</b> waist-to-hip ratio $> 0.9$ for males, $> 0.85$ for females
Elevated triglycerides $\geq 150$ mg/dl	Elevated triglycerides $\geq 150$ mg/dl	Dislipidemia with either or both: Elevated triglycerides $\geq 150$ mg/dl
Low HDL cholesterol $< 40$ mg/dl for males, $< 50$ mg/dl for females	Low HDL cholesterol $< 35$ mg/dl for males, $< 40$ mg/dl for females	Low HDL cholesterol $< 35$ mg/dl for males, $< 40$ mg/dl for females
	Microalbuminuria $> 20$ $\mu$ g/min or albumin-to-creatinine ratio $\geq 20$ mg/g	

\*Modified as described in the Kuopio study.<sup>9</sup>

genism. It has been described poetically as “the thief of womanhood”<sup>10</sup> because women with PCOS seek medical attention for infertility and hirsutism. Characteristics of PCOS are summarized in Table 2.

That PCOS also conveys significant risks for diabetes and endometrial cancer is a fact that has been clinically under-recognized. PCOS may also be associated with an increased risk for CVD; several studies have shown increased markers of CVD, usually in relation to features of the metabolic syndrome. Many women with PCOS have additional features of the metabolic syndrome, especially insulin resistance and obesity.

Women with PCOS have a higher prevalence and a greater degree of hyperinsulinemia<sup>11,12</sup> and insulin resistance<sup>13–15</sup> than weight-matched control subjects. Of women who have PCOS, as many as 30% have impaired glucose tolerance (IGT) and an additional 7.5%

have diabetes.<sup>16</sup> Even among nonobese women with PCOS, 10.3% have IGT, and 1.5% have diabetes.<sup>16</sup> In long-term follow-up, 16% of women who had been treated for PCOS 20–30 years earlier had developed diabetes by the age of menopause.<sup>17</sup> The etiology of the insulin resistance is unclear, but suppression of the excess androgens does not alter the insulin resistance.<sup>18,19</sup>

Insulin resistance is worsened by the coexistence of obesity, which is also increased in the PCOS population.<sup>20</sup> More than 40% of PCOS patients are obese.<sup>21,22</sup> The insulin resistance is disproportionate to the obesity, however. Obese women with PCOS have greater insulin resistance than weight-matched control subjects or lean PCOS subjects.<sup>13,14</sup> This is associated with differences in fat distribution. Even in individuals with a nonobese BMI, a higher waist-to-hip ratio is seen in those with PCOS compared to those without

PCOS.<sup>23</sup> This is supported by the higher proportion of visceral adiposity measured by ultrasound in lean PCOS patients compared to weight-matched control subjects.<sup>24</sup>

Obesity also exacerbates several other metabolic abnormalities in PCOS. In comparison to lean women with PCOS, obese women with PCOS have higher levels of testosterone and lower levels of luteinizing hormone.<sup>25–27</sup>

Obese women with PCOS also have a dyslipidemia. At least one abnormal lipid level is seen in 70% of women with PCOS.<sup>28</sup> The pattern of dyslipidemia found in the metabolic syndrome, which features elevated triglycerides and low HDL cholesterol, has been reported in association with obesity in PCOS, but this has not been found to differ from weight-matched control subjects.<sup>29</sup> Studies controlling for insulin resistance have found that the low HDL cholesterol and high triglycerides are associated with

**Table 2. Features of Polycystic Ovary Syndrome**

By definition:

- Oligomenorrhea
- Hyperandrogenism: acne or hirsutism, or
- Hyperandrogenemia: elevated total or free testosterone or DHEA-S

Also frequently seen:

- Insulin resistance
- Hyperinsulinemia
- Elevated LH:FSH ratio
- Abdominal obesity
- Polycystic ovaries by ultrasound\*
- Infertility

DHEA-S, dihydroepiandrosterone-sulfate; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

\*Polycystic ovaries are not part of the definition of PCOS because they are also found in 24% of normal cycling, nonhyperandrogenic women.<sup>84</sup>

insulin resistance rather than with the presence of PCOS.<sup>30</sup> Abnormalities of LDL cholesterol have not been found consistently in PCOS.<sup>31</sup> However, even in those with a normal LDL level, Pirwany et al.<sup>32</sup> have shown increased VLDL and small, dense LDL cholesterol in PCOS relative to control subjects, as is seen in the metabolic syndrome.<sup>33</sup>

The final facet of the metabolic syndrome, hypertension, is uncommon in PCOS.<sup>31,34</sup> However, this may be a matter of exposure. In a retrospective study, women treated 20–30 years for PCOS were found to have an increased prevalence of both hypertension and diabetes compared to weight-matched control subjects.<sup>17,35</sup> In addition, some studies of 24-hour ambulatory systolic blood pressure recordings in young women with PCOS show increases that are predictive of the development of hypertension later in life.<sup>36</sup> Thus, several features of the metabolic syndrome overlap with features of PCOS.

In women with obesity, there may be an adverse clinical synergy between features of both PCOS and the metabolic syndrome. Both of these conditions could predispose to CVD through common pathways.

The risk for CVD in the metabolic syndrome is well supported by large epidemiological studies. In PCOS, retro-

spective studies based on menstrual abnormalities (which would mostly, but not exclusively, be caused by PCOS) show increased cardiovascular and diabetes-related deaths.<sup>37,38</sup> One challenge of these studies is the time lag between reproductive symptoms heralding PCOS and much later development of CVD.

An assessment of women undergoing coronary angiography for chest pain found an excess of women with polycystic ovaries seen on ultrasound.<sup>39</sup> While neither endpoint—the need for angiography or the presence of polycystic-appearing ovaries—is specific, this has encouraged others to look more closely. Coronary artery calcification was increased when examined in small studies of women with PCOS.<sup>40,41</sup>

In classically defined PCOS, many risk factors, such as dyslipidemia and hypertension, and markers of CVD have been found. Models based on the combined risk factors of the metabolic syndrome in PCOS, such as obesity, diabetes, dyslipidemia, and hypertension, predict a sevenfold increased risk of myocardial infarction in women with PCOS compared to age-matched control subjects.<sup>42</sup> However, as carefully reviewed by Legro,<sup>43</sup> not all women with PCOS have the metabolic syndrome, and prospective data do not yet support an increased occurrence of CVD in all

women with PCOS. These issues may be increasingly difficult to resolve because current therapies for PCOS also affect known metabolic risk factors.

**Therapeutic Overlap**

Is it important to identify women with PCOS and the metabolic syndrome in order to target early intervention? This question can best be addressed by considering separately two subsets of PCOS: those with diabetes and those with other metabolic features including standard symptoms of PCOS, such as infertility, oligomenorrhea, and hirsutism. In the former set, therapies for diabetes with dual effects in PCOS and the metabolic syndrome should be the first approach. In the latter patients, the chief complaint can be targeted using a broader range of therapeutics.

**Women with PCOS features who already have diabetes**

Up to 27% of premenopausal women with type 2 diabetes also have PCOS.<sup>44</sup> This is interesting for two reasons: first, it emphasizes the potential severity of the insulin resistance in PCOS, and second, it shows that insulin resistance itself does not lead to PCOS in the majority of women with type 2 diabetes.

For those women with both PCOS and diabetes, specific therapies can address features of both diseases, especially those exacerbated by insulin resistance. Reducing hyperinsulinemia and insulin resistance has been shown to improve the defining features of PCOS—increasing menstrual cyclicity and decreasing hyperandrogenism.

It is essential to identify those patients with both PCOS and diabetes not only to tailor their therapies, but also to introduce the appropriate preventive screening and treatment for known cancer risks. The risk of endometrial cancer is increased in type 2 diabetes and in PCOS.<sup>35</sup> In diabetes, epidemiological studies link this risk closely with obesity.<sup>45–47</sup> In PCOS, obesity, hyperinsulinemia, and anovulation have been associated with the increased risk.<sup>48</sup> In

addition to regular Pap smears, PCOS therapies have focused on increasing menstrual regularity to decrease this risk. Many mechanisms that decrease insulin resistance also improve menstrual function. This raises an important and as yet unanswered question: are any diabetes therapies better for women with PCOS?

**Weight loss.** The safest and cheapest therapy that has shown benefit both in diabetes and PCOS is weight loss by lifestyle modification. The observation that weight gain often preceded the development of hyperandrogenism and oligomenorrhea led to early approaches to treat PCOS by weight reduction. Many small studies have shown that even modest weight loss (10–20%) improves all symptoms of PCOS in obese patients: acne, hirsutism, and menstrual irregularities.<sup>49–54</sup> The improvements are likely a result of the reductions in insulin levels and insulin resistance also measured in these studies. Weight loss was accomplished by using hypocaloric diets, usually 1,000–1,200 kcal/day for as little as 8 weeks.

In diabetes and the metabolic syndrome, weight loss is also associated with improvements in other features of the metabolic syndrome, including dyslipidemia and hypertension.<sup>55</sup> Although dietary restriction-induced weight loss offers significant advantages as a treatment for both diabetes and PCOS, it is notoriously difficult to achieve.

Altered dietary composition is also useful. Fiber slows nutrient absorption after meals and reduces insulin secretion. Increased dietary fiber intake has been shown to improve insulin resistance in healthy adults<sup>56</sup> and in diabetes<sup>57</sup> but has not yet been separately assessed in PCOS. Reduction in digestible dietary carbohydrate, as in the popular Atkins diet, has been shown to be safe and effective in obese patients, with improvement in insulin response to glucose load, diastolic blood pressure, and dyslipidemia, increasing HDL cholesterol and decreasing triglycerides.<sup>58,59</sup> In PCOS, when low- and high-protein isocaloric diets were compared, both resulted in

equal weight loss and improvement in insulin levels, insulin response to a meal, total cholesterol, triglycerides, and LDL, although HDL was slightly decreased on the low-protein diet.<sup>60</sup> Thus, the benefits derive from weight loss more than from the specific mechanism by which that loss is achieved.

Eating dynamics, such as binge eating, can increase insulin secretion and insulin resistance.<sup>61</sup> This is problematic because of the increased incidence of eating disorders in both diabetes and PCOS.<sup>62–65</sup> Eating disorders may contribute to difficulties with sustaining weight loss.

Given the significant effects of modest weight loss on features of both PCOS and the metabolic syndrome, it is tempting to consider more interventional approaches to weight loss when caloric restriction fails. In the subset of patients with diabetes and obesity, several other options have been proven effective.

Weight loss medications, including phenteramine (for short-term use) and sibutramine and orlistat (for long-term use), are recommended for individuals with a BMI > 30 kg/m<sup>2</sup> or lower if comorbidities such as diabetes are present. (Sibutramine must be used very carefully if hypertension is present.) In separate trials in diabetes or dyslipidemia, both sibutramine and orlistat caused weight loss with improvements in hyperinsulinemia and dyslipidemia, although sibutramine was associated with an increase in blood pressure.<sup>66–68</sup> Just as lifestyle modifications must be maintained to prevent weight regain, sibutramine and orlistat usually need to be continued. Neither drug has been studied yet in PCOS without these other comorbidities, though the improvement in insulin resistance suggests that they would be useful for obese women with PCOS.

For patients with diabetes and a BMI > 35 kg/m<sup>2</sup>, bariatric surgery may also be an appropriate intervention. Weight loss after bariatric surgery also leads to improvements in insulin resistance, hypertension, and dyslipidemia. Again,

while important for the management of diabetes and obesity, the effects on features of PCOS have not been examined.

**Exercise.** As a lifestyle modification, physical exercise helps sustain weight loss, but it also has benefits independent of weight loss. Exercise can increase glucose disposal and muscle sensitivity to insulin. In PCOS, women who self-reported 8 hours of sports activities per week had improvement in acne and menstrual irregularities.<sup>69</sup> Exercise as the primary intervention without attendant weight loss (< 5% weight loss) improved insulin sensitivity and free testosterone index and induced ovulation in 9 of 18 obese PCOS patients.<sup>70</sup> Clearly, a reasonable regimen of exercise (see the Diabetes Prevention Program [DPP] regimen below), in addition to modifications of diet, is a prudent recommendation for patients with PCOS.

**Medical therapies for insulin resistance.** Two major pharmacological approaches to the treatment of diabetes have also revolutionized the therapy of PCOS. These are the insulin sensitizers: the biguanide metformin and the thiazolidinediones troglitazone (no longer available), pioglitazone, and rosiglitazone. These agents improve not only glucose control, but also the reproductive abnormalities associated with PCOS.

Metformin increases peripheral glucose uptake and decreases hepatic glucose production. The major advantage in patients with diabetes and PCOS is that metformin is one of only two diabetes medications that do not cause weight gain.

Harborne et al.<sup>71</sup> have recently reviewed the seven randomized placebo-controlled trials (six of which were double-blinded) of metformin in PCOS. This analysis showed improvements in metabolic syndrome features that included weight loss (4%) and decreased insulin levels (27%). Several of these studies also noted improvements in dyslipidemia, with an increased HDL and a decreased LDL cholesterol. In terms of PCOS features, androgens decreased (21%), menstrual cyclicity improved

(50%), and acne decreased (in one study).<sup>71</sup> Notably, hirsutism improved significantly in only three of six trials that evaluated hirsutism, although most were too short to determine changes in hair growth. Major side effects were nausea and diarrhea, which are also seen with metformin therapy in diabetes.

The thiazolidinedione class works at the level of the peroxisome proliferator-activated receptor gamma to directly improve insulin action. These drugs decrease insulin resistance and hyperinsulinemia and improve dyslipidemia and blood pressure in patients with diabetes or IGT.<sup>72</sup> Troglitazone, which has now been withdrawn from the market because of reports of hepatotoxicity, was studied extensively in nondiabetic PCOS patients.<sup>73</sup> It improved ovulation, hirsutism, hyperandrogenemia, and insulin resistance despite an average 1-kg weight gain. The newer congeners pioglitazone and rosiglitazone are effective for the metabolic syndrome and diabetes and in small studies have worked well for PCOS symptoms of menstrual irregularity and hyperandrogenism.<sup>74–76</sup>

Antidiabetic therapy such as acarbose should be considered second-line because, although it reduces insulin requirements by decreasing absorption of ingested carbohydrate, it does not decrease insulin resistance. It also does not affect obesity. Acarbose has been tested in one small study of hyperinsulinemic women with PCOS and has demonstrated effectiveness in reducing hirsutism and acne scores as well as postprandial glucose and insulin responses.<sup>77</sup>

Insulin does not improve chronic insulin resistance. Therefore, there is no apparent benefit to this therapy for women with PCOS who do not have diabetes, although the use of insulin specifically in PCOS has not been studied. Its use should be limited to women with diabetes and PCOS whose diabetes does not respond to the above oral agents (or who cannot tolerate them). As in any diabetic patient with extremely high blood glucose levels, in women with PCOS and diabetes, the short-term use

of insulin may be necessary for immediate safety concerns to avoid dehydration and related complications. Insulin use also causes weight gain and therefore is not the best therapy for such women with early diabetes who are still producing excess insulin.

As with insulin, sulfonylureas act by augmenting insulin secretion rather than treating the primary pathology of insulin resistance. Therefore, they are not an appropriate therapy for women with both diabetes and PCOS.

**Pregnancy concerns.** The risks of these therapies in relation to their benefits for PCOS must be considered, especially in pregnancy. Because PCOS patients are by definition premenopausal, pregnancy is a significant issue, and in many cases, infertility is the chief complaint. Metformin increases ovulation rapidly (as early as 3 months), modestly (increasing from one to two ovulations per 5 months), and without weight loss.<sup>71</sup> It has also improved spontaneous pregnancy rates, and contraception is recommended for women who do not wish to become pregnant.

Women must be informed about this increased probability of conception and the risk of continuing metformin during pregnancy. Data about the safety of metformin in early pregnancy are conflicting regarding possible protection from early pregnancy loss. There is no evidence of animal or human teratogenicity (pregnancy category B). In mothers with diabetes, metformin has been used in the second and third trimesters without conclusive evidence of increased perinatal morbidity, although Coetzee et al.<sup>78</sup> reported an increase in neonatal jaundice. Another study comparing metformin to sulfonylurea treatment in pregnancy did show a modest increase in perinatal mortality and pre-eclampsia, but these results were confounded by a higher BMI and age in the metformin group. Thus, further studies of metformin in pregnancy are needed, and current recommendations are to discontinue use as soon as pregnancy is established.

Thiazolidinediones, on the other hand, are known teratogens that exhibit profound effects on cellular differentiation with documented teratogenicity and lethality in animal studies (pregnancy category C). They have the additional disadvantage of a slow metabolic clearance and may take months to be eliminated from the body. Despite the controlled setting of a major study of troglitazone, 5.9% of subjects had unexpected pregnancies in the treatment arms, highlighting the need for counseling and contraception.<sup>73</sup> Therefore, the thiazolidinediones must be stringently avoided in women who might become pregnant. Most insulins are safe for use and are the preferred therapy for diabetes in pregnancy.

An important but overlooked consideration is the medical risk of facilitating pregnancy in women with severe diabetes or obesity. The intending mother must be made aware of the increased risk of pregnancy to her health and that of her baby based on the severity of her diabetes, obesity, or hypertension. Having said this, most women with PCOS can have successful pregnancies without a dramatic increase in health risk, and the risks of pregnancy from diabetes and obesity can be minimized with good pre-pregnancy counseling and care.

### **Women with PCOS but without diabetes**

The metabolic syndrome by definition is associated with an increased risk of CVD. Treatment of the individual components of the syndrome, including dyslipidemia, obesity, and hypertension, clearly decrease CVD. Data from the DPP have demonstrated the powerful effects of treating insulin resistance in patients at high risk of developing diabetes.<sup>79</sup> Should women with PCOS be treated for insulin resistance alone (when infertility, oligomenorrhea, and hirsutism do not require treatment)? In this situation, the risks must be balanced with potential side effects and the need for monitoring in this young population. PCOS patients have distinct worsening

with obesity and should be especially counseled not to gain excess weight. Lifestyle alterations and weight loss when indicated reduce insulin resistance and offer multiple benefits. Medical therapies are not only less effective, but also carry risks.

As the DPP has recently shown, the most effective method to prevent progression from IGT to overt diabetes is lifestyle modification through exercise and diet.<sup>79</sup> The lifestyle arm of the DPP included dietary education, weight loss counseling, and 150 minutes of exercise per week, resulting in a net loss of 7% body weight and a 58% reduction in the progression to diabetes.<sup>79</sup> The metformin arm, while effective, only reduced the progression to diabetes by 21%.<sup>79</sup>

Metformin has also been used to treat the metabolic syndrome in the absence of diabetes. Landin et al.<sup>80</sup> used metformin in patients with insulin resistance and hypertension and found improvements in both as well as in dyslipidemia. Metformin is also effective in the treatment of some PCOS features. It modestly increases menstrual regularity and ovulation and decreases weight without clearly improving hirsutism.<sup>71</sup> Lean women with PCOS also improve insulin resistance and hyperandrogenism without changing BMI on metformin.<sup>81</sup> Because of these benefits and its relative safety before pregnancy, metformin is a useful adjunct to lifestyle changes for women with complaints of menstrual irregularity or infertility, but not for those complaining of hirsutism.

Except in women who are sterile, the thiazolidinediones must be used cautiously. As noted above, these medications are very effective for PCOS symptoms and insulin resistance, and improvement in these parameters may lead to increased ovulation. In the Azziz study of 305 women with PCOS, there were 16 unexpected pregnancies despite counseling to avoid pregnancy and the requirement for contraception.<sup>73</sup> No excess of elevated liver function test results were seen among these women.

The newer thiazolidinediones have not been studied as extensively in PCOS without diabetes. Pioglitazone reduced hyperandrogenism but was more effective at increasing ovulation in women with PCOS who were obese and insulin resistant than in those with obesity and normal insulin sensitivity.<sup>75</sup> Rosiglitazone has also been shown to increase ovulation and decrease hyperandrogenism.<sup>74,76</sup>

For women at risk for unplanned pregnancy who complain of irregular periods or hirsutism, combination estrogen/progestin contraceptives are the safest treatment and will also ameliorate hyperandrogenism without affecting insulin resistance. Anti-androgen therapy, such as spironolactone, can be added for further treatment of hirsutism.

New agents under investigation for use in PCOS include pramlintide and *D-chiro*-inositol. Pramlintide is an analog of amylin, a  $\beta$ -cell hormone that is normally cosecreted with insulin; it complements the effects of insulin in postprandial glucose control, in part by suppressing glucagon secretion. In type 1 and late type 2 diabetes, pramlintide improves postprandial glucose excursions, but its use so far has been in insulin- and amylin-deficient settings.<sup>82</sup> *D-chiro*-inositol is an insulin sensitizer that has preliminarily been shown to increase ovulation in PCOS.<sup>83</sup> Ovulation induction is the major area of PCOS treatment for which more effective therapies are needed.

### Summary

Unlike the metabolic syndrome with its largely asymptomatic risk factors, PCOS presents with overt symptoms of infertility, hirsutism, and acne. Although these are the problems that bring women to health care providers' attention, their presence affords providers the opportunity to intervene early with counseling and, if needed, medications to alter the risk profile for later development of the metabolic syndrome or CVD.

However, there is also a deficit of long-term outcome information, and certainly risk factors do not always progress

to disease. Therefore, the prudent approach requires emphasis on the modification of lifestyle factors such as diet and exercise to modify risk factors not yet reaching clinical disease.

In the subset of patients with PCOS and diabetes, tailored therapies that target the multiple abnormalities, particularly insulin resistance, are indicated. The role of medical therapy for insulin resistance or the metabolic syndrome in nondiabetic patients with PCOS is presently unclear.

### REFERENCES

- <sup>1</sup>Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
- <sup>2</sup>Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
- <sup>3</sup>Reaven GM: Banting lecture: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
- <sup>4</sup>Balkau B, Charles MA: Comment on the provisional report from the WHO consultation. *Diabet Med* 16:442–443, 1999
- <sup>5</sup>Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
- <sup>6</sup>The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
- <sup>7</sup>Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289:2560–2572, 2003
- <sup>8</sup>Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ: Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 73:460–468, 1994
- <sup>9</sup>Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
- <sup>10</sup>Kitzinger C, Willmott J: 'The thief of womanhood': women's experience of polycystic ovarian syndrome. *Soc Sci Med* 54:349–361, 2002

- <sup>11</sup>Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A: Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. *J Clin Endocrinol Metab* 65:499–507, 1987
- <sup>12</sup>Conway GS, Jacobs HS, Holly JM, Wass JA: Effects of luteinizing hormone, insulin, insulin-like growth factor-I and insulin-like growth factor small binding protein 1 in the polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 33:593–603, 1990
- <sup>13</sup>Dunaif A, Segal KR, Futterweit W, Dobrjansky A: Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 38:1165–1174, 1989
- <sup>14</sup>Rajkhowa M, Bicknell J, Jones M, Clayton RN: Insulin sensitivity in women with polycystic ovary syndrome: relationship to hyperandrogenemia. *Fertil Steril* 61:605–612, 1994
- <sup>15</sup>Morales AJ, Laughlin GA, Butzow T, Maheshwari H, Baumann G, Yen SS: Insulin, somatotrophic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. *J Clin Endocrinol Metab* 81:2854–2864, 1996
- <sup>16</sup>Legro RS, Kuneselman AR, Dodson WC, Dunaif A: Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 84:165–169, 1999
- <sup>17</sup>Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Oden A, Janson PO, Mattson LA, Crona N, Lundberg PA: Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. *Fertil Steril* 57:505–513, 1992
- <sup>18</sup>Dunaif A, Green G, Futterweit W, Dobrjansky A: Suppression of hyperandrogenism does not improve peripheral or hepatic insulin resistance in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 70:699–704, 1990
- <sup>19</sup>Geffner ME, Kaplan SA, Bersch N, Golde DW, Landaw EM, Chang RJ: Persistence of insulin resistance in polycystic ovarian disease after inhibition of ovarian steroid secretion. *Fertil Steril* 45:327–333, 1986
- <sup>20</sup>Stein IF, Leventhal ML: Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 29:181–191, 1935
- <sup>21</sup>Franks S: Polycystic ovary syndrome: a changing perspective. *Clin Endocrinol (Oxf)* 31:87–120, 1989
- <sup>22</sup>Carmina E, Lobo RA: Polycystic ovary syndrome (PCOS): arguably the most common endocrinopathy is associated with significant morbidity in women. *J Clin Endocrinol Metab* 84:1897–1899, 1999
- <sup>23</sup>Vrbikova J, Bendlova B, Hill M, Vankova M, Vondra K, Starka L: Insulin sensitivity and beta-cell function in women with polycystic ovary syndrome. *Diabetes Care* 25:1217–1222, 2002
- <sup>24</sup>Yildirim B, Sabir N, Kaleli B: Relation of intra-abdominal fat distribution to metabolic disorders in nonobese patients with polycystic ovary syndrome. *Fertil Steril* 79:1358–1364, 2003
- <sup>25</sup>Laatikainen T, Tulenheimo A, Andersson B, Karkkainen J: Obesity, serum steroid levels, and pulsatile gonadotropin secretion in polycystic ovarian disease. *Eur J Obstet Gynecol Reprod Biol* 15:45–53, 1983
- <sup>26</sup>Conway GS, Honour JW, Jacobs HS: Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. *Clin Endocrinol (Oxf)* 30:459–470, 1989
- <sup>27</sup>Holte J, Bergh T, Gennarelli G, Wide L: The independent effects of polycystic ovary syndrome and obesity on serum concentrations of gonadotrophins and sex steroids in premenopausal women. *Clin Endocrinol (Oxf)* 41:473–481, 1994
- <sup>28</sup>Legro RS, Kuneselman AR, Dunaif A: Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 111:607–613, 2001
- <sup>29</sup>Holte J, Bergh T, Berne C, Lithell H: Serum lipoprotein lipid profile in women with the polycystic ovary syndrome: relation to anthropometric, endocrine and metabolic variables. *Clin Endocrinol (Oxf)* 41:463–471, 1994
- <sup>30</sup>Robinson S, Henderson AD, Gelding SV, Kiddy D, Nithithyanathan R, Bush A, Richmond W, Johnston DG, Franks S: Dyslipidaemia is associated with insulin resistance in women with polycystic ovaries. *Clin Endocrinol (Oxf)* 44:277–284, 1996
- <sup>31</sup>Sampson M, Kong C, Patel A, Unwin R, Jacobs HS: Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without the polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 45:623–629, 1996
- <sup>32</sup>Pirwany IR, Fleming R, Greer IA, Packard CJ, Sattar N: Lipids and lipoprotein subfractions in women with PCOS: relationship to metabolic and endocrine parameters. *Clin Endocrinol (Oxf)* 54:447–453, 2001
- <sup>33</sup>Edwards KL, Austin MA, Newman B, Mayer E, Krauss RM, Selby JV: Multivariate analysis of the insulin resistance syndrome in women. *Arterioscler Thromb* 14:1940–1945, 1994
- <sup>34</sup>Zimmermann S, Phillips RA, Dunaif A, Finegood DT, Wilkenfeld C, Ardeljan M, Gorlin R, Krakoff LR.: Polycystic ovary syndrome: lack of hypertension despite profound insulin resistance. *J Clin Endocrinol Metab* 75:508–513, 1992
- <sup>35</sup>Wild S, Pierpoint T, Jacobs H, McKeigue P: Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)* 3:101–105, 2000
- <sup>36</sup>Holte J, Gennarelli G, Berne C, Bergh T, Lithell H: Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? *Hum Reprod* 11:23–28, 1996
- <sup>37</sup>Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS: Mortality of women with polycystic ovary syndrome at long-term follow-up. *J Clin Epidemiol* 51:581–586, 1998
- <sup>38</sup>Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, Speizer FE, Manson JE: Menstrual cycle irregularity and risk for future cardiovascular disease. *J Clin Endocrinol Metab* 87:2013–2017, 2002
- <sup>39</sup>Birdsall MA, Farquhar CM, White HD: Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. *Ann Intern Med* 126:32–35, 1997
- <sup>40</sup>Talbott EO, Zborowski JV, Sutton-Tyrrell K, McHugh-Pemu KP, Guzick DS: Cardiovascular risk in women with polycystic ovary syndrome. *Obstet Gynecol Clin North Am* 28:111–133, vii, 2001
- <sup>41</sup>Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd, Fitzpatrick LA: Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:2562–2568, 2003
- <sup>42</sup>Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A: Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand* 71:599–604, 1992
- <sup>43</sup>Legro RS: Polycystic ovary syndrome and cardiovascular disease: a premature association? *Endocrine Rev* 24:302–312, 2003
- <sup>44</sup>Peppard HR, Marfori J, Iuorno MJ, Nestler JE: Prevalence of polycystic ovary syndrome among premenopausal women with type 2 diabetes. *Diabetes Care* 24:1050–1052, 2001
- <sup>45</sup>Brinton LA, Berman ML, Mortel R, Twigg LB, Barrett RJ, Wilbanks GD, Lannom L, Hoover RN: Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. *Am J Obstet Gynecol* 167:1317–1325, 1992
- <sup>46</sup>La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P: A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 70:950–953, 1994
- <sup>47</sup>Shoff SM, Newcomb PA: Diabetes, body size, and risk of endometrial cancer. *Am J Epidemiol* 148:234–240, 1998
- <sup>48</sup>Hardiman P, Pillay OS, Atiomo W: Polycystic ovary syndrome and endometrial carcinoma. *Lancet* 361:1810–1812, 2003
- <sup>49</sup>Harlass FE, Plymate SR, Fariss BL, Belts RP: Weight loss is associated with correction of gonadotropin and sex steroid abnormalities in the obese anovulatory female. *Fertil Steril* 42:649–652, 1984
- <sup>50</sup>Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, Franks S: Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 36:105–111, 1992
- <sup>51</sup>Guzick DS, Wing R, Smith D, Berga SL, Winters SJ: Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertil Steril* 61:598–604, 1994
- <sup>52</sup>Holte J, Bergh T, Berne C, Wide L, Lithell H: Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 80:2586–2593, 1995
- <sup>53</sup>Jakubowicz DJ, Nestler JE: 17 alpha-Hydroxyprogesterone responses to leuprolide and serum androgens in obese women with and without polycystic ovary syndrome offer dietary

weight loss. *J Clin Endocrinol Metab* 82:556–560, 1997

<sup>54</sup>Wahrenberg H, Ek I, Reynisdottir S, Carlstrom K, Bergqvist A, Arner P: Divergent effects of weight reduction and oral contraception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 84:2182–2187, 1999

<sup>55</sup>Case CC, Jones PH, Nelson K, O'Brian Smith E, Ballantyne CM: Impact of weight loss on the metabolic syndrome. *Diabetes Obes Metab* 4:407–414, 2002

<sup>56</sup>Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL: High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. *Am J Clin Nutr* 52:524–528, 1990

<sup>57</sup>Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ: Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 342:1392–1398, 2000

<sup>58</sup>Westman EC, Yancy WS, Edman JS, Tomlin KF, Perkins CE: Effect of 6-month adherence to a very low carbohydrate diet program. *Am J Med* 113:30–36, 2002

<sup>59</sup>Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S: A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 348:2082–2090, 2003

<sup>60</sup>Moran LJ, Noakes M, Clifton PM, Tomlinson L, Norman RJ: Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:812–819, 2003

<sup>61</sup>Pasquali R, Casimirri F: The impact of obesity on hyperandrogenism and polycystic ovary syndrome in premenopausal women. *Clin Endocrinol (Oxf)* 39:1–16, 1993

<sup>62</sup>Peveler RC, Fairburn CG, Boller I, Dunger D: Eating disorders in adolescents with IDDM: A controlled study. *Diabetes Care* 15:1356–1360, 1992

<sup>63</sup>Stancin T, Link DL, Reuter JM: Binge eating and purging in young women with IDDM. *Diabetes Care* 12:601–603, 1989

<sup>64</sup>McCluskey SE, Lacey JH, Pearce JM: Binge-eating and polycystic ovaries. *Lancet* 340:723, 1992

<sup>65</sup>McCluskey S, Evans C, Lacey JH, Pearce JM, Jacobs H: Polycystic ovary syndrome and bulimia. *Fertil Steril* 55:287–291, 1991

<sup>66</sup>Scheen AJ, Ernest P: New antiobesity agents in type 2 diabetes: overview of clinical trials with sibutramine and orlistat. *Diabetes Metab* 28:437–445, 2002

<sup>67</sup>Dujovne CA, Zavoral JH, Rowe E, Mendel CM: Effects of sibutramine on body weight and serum lipids: a double-blind, randomized, placebo-controlled study in 322 overweight and obese patients with dyslipidemia. *Am Heart J* 142:489–497, 2001

<sup>68</sup>Lucas CP, Boldrin MN, Reaven GM: Effect of orlistat added to diet (30% of calories from fat) on plasma lipids, glucose, and insulin in obese patients with hypercholesterolemia. *Am J Cardiol* 91:961–964, 2003

<sup>69</sup>van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasig RA, Koppenaal C, Schoemaker J: Polycystic ovaries in adolescents and the relationship with menstrual cycle patterns, luteinizing hormone, androgens, and insulin. *Fertil Steril* 74:49–58, 2000

<sup>70</sup>Huber-Buchholz MM, Carey DG, Norman RJ: Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* 84:1470–1474, 1999

<sup>71</sup>Harborne L, Fleming R, Lyall H, Norman J, Sattar N: Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 361:1894–1901, 2003

<sup>72</sup>Braunstein S: Cardiovascular disease and benefits of thiazolidinediones. *Postgrad Med Spec No*:45–52, 2003

<sup>73</sup>Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, O'Keefe M, Ghazzi MN: Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 86:1626–1632, 2001

<sup>74</sup>Ghazeeri G, Kutteh WH, Bryer-Ash M, Haas D, Ke RW: Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome. *Fertil Steril* 79:562–566, 2003

<sup>75</sup>Romualdi D, Guido M, Ciampelli M, Giuliani M, Leoni F, Perri C, Lanzone A: Selective effects of pioglitazone on insulin and androgen

abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. *Hum Reprod* 18:1210–1218, 2003

<sup>76</sup>Shobokshi A, Shaarawy M: Correction of insulin resistance and hyperandrogenism in polycystic ovary syndrome by combined rosiglitazone and clomiphene citrate therapy. *J Soc Gynecol Invest* 10:99–104, 2003

<sup>77</sup>Ciotta L, Calogero AE, Farina M, De Leo V, La Marca A, Cianci A: Clinical, endocrine and metabolic effects of acarbose, an alpha-glucosidase inhibitor, in PCOS patients with increased insulin response and normal glucose tolerance. *Hum Reprod* 16:2066–2072, 2001

<sup>78</sup>Coetzee EJ, Jackson WP: Metformin in management of pregnant insulin-independent diabetics. *Diabetologia* 16:241–245, 1979

<sup>79</sup>Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002

<sup>80</sup>Landin K, Tengborn L, Smith U: Treating insulin resistance in hypertension with metformin reduces both blood pressure and metabolic risk factors. *J Intern Med* 229:181–187, 1991

<sup>81</sup>Nestler JE, Jakubowicz DJ: Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. *J Clin Endocrinol Metab* 82:4075–4079, 1997

<sup>82</sup>Moyses C, Young A, Kolterman O: Modulation of gastric emptying as a therapeutic approach to glycaemic control. *Diabet Med* 13:S34–S38, 1996

<sup>83</sup>Nestler JE, Stovall D, Akhter N, Iuorno MJ, Jakubowicz DJ: Strategies for the use of insulin-sensitizing drugs to treat infertility in women with polycystic ovary syndrome. *Fertil Steril* 77:209–215, 2002

<sup>84</sup>Polson DW, Adams J, Wadsworth J, Franks S: Polycystic ovaries—a common finding in normal women. *Lancet* 1:870–872, 1988

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